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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,517	03/16/2004	Xiaoyang Qi	0010872.0556916	4062

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EXAMINER	
SANG, HONG	
ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
03/26/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@fbtlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/801,517	QI, XIAOYANG	
	Examiner	Art Unit	
	HONG SANG	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *9-43,58 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 44-57, 59-63 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RE: Qi

1. The finality of the previous office action is withdrawn in view of panel decision from Pre-Appeal Brief Review. Prosecution on the merits continues.

2. Claims 1-65 are pending. Claims 9-43, 58 and 64 have been withdrawn from consideration as being drawn to non-elected inventions.

3. Claims 1-8, 44-57, 59-63 and 65 are under examination.

4. It is noted that applicant has identified claims 44-49, 59-63 and 65 as withdrawn. However, these claims have not been withdrawn by the examiner.

Rejections Maintained

Claim Rejections - 35 USC § 112, 1st paragraph (Written Description)

5. The rejection of claims 1-8, 50-57, 59-63, and 65 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

The response states that the saposin fold comprises five alpha-helices (H1 through H5), which are responsible for proper orientation within the phospholipid bilayer of the nanovesicles and further comprise the enzyme activation of domain of amino acids 48-62, which span helices H3 and H4. The consensus sequence is described (Qi et al 1996) and the level of conservation here is very high, with 6 conserved, 7 fairly conserved. The prior art and the previous 1.132 Declarations show that the five alpha-helices (H 1 through H5) are required for the function of retaining not just plasma membrane affinity but an anti-tumor activity as well. In addition, it is well within the

capability of one of ordinary skill in the art, through routine laboratory procedures, to ascertain whether or not a given polypeptide retains plasma-membrane affinity and whether or not a given nanovesicle exhibits anti- tumor activity. The disclosure of sequences and domain sites further provides meaningful, specific guidance that would allow one of ordinary skill in the art to "immediately envisage" the claimed invention.

In light of panel decision from Pre-Appeal Brief Review, the rejection made to the part (a) of claim 1 and part (i) of claim 50 (i.e. a polypeptide having an amino acid sequence at least 95% identical to SEQ ID NO:2) is withdrawn. However, the rejection made to the part (b) of claim 1 and part (ii) of claim 50 (i.e. a polypeptide having an amino acid sequence as set forth in SEQ ID NO:2 and having one or more conservative substitutions) is maintained (emphasis added).

Applicant's arguments do not overcome the rejection to the part (b) of claim 1 and part (ii) of claim 50 for the reasons of record. Specifically the phrase "one or more conservative substitution" encompasses a change of one up to all amino acids of the SEQ ID NO: 2. Substitution many amino acid residues together would likely to affect the protein's structure, and thereby the function. The specification does not provide adequate written description regarding which amino acids and how many of them can be changed in the wild type saposin C such that the resulting variants still have the anti-tumor activity. Based on the unpredictability of protein chemistry, and lack of written description, those of ordinary skill in the art would not be able to envision the detailed structures of the encompassed variants, as such one skilled in the art would reasonable

conclude that the applicant was not in possession of the variants as broadly claimed in part (b) of the claims.

Applicant can overcome the rejection by cancelling the part (b) of claim 1 and part (ii) of claim 50, or amending part (b) of claim 1 and part (ii) of claim 50 to further include a limitation of "at least 95% identical to SEQ ID NO:2".

It is noted that claims 59-63 and 69 (which were not rejected in the previous office action) are now included in this rejection for the recitation of "a biologically active variant of the amino acid sequence set forth in SEQ ID NO:1, the amino acid sequence set forth in SEQ ID NO:1 having one or more conservative substitutions" and "a biologically active variant of the amino acid sequence set forth in SEQ ID NO:2, the amino acid sequence set forth in SEQ ID NO:1 having one or more conservative substitutions". The specification defines biologically active variants of a native prosaposin protein of the invention as variants having at least about 80%, 85%, preferably at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, and more preferably at least about 98%, 99% or more sequence identity to the amino acid sequence for the native protein, or may differ from that protein by as few as 1-15 amino acid residues, as few as 1-10, such as 6-10, as few as 5, as few as 4, 3, 2, or even 1 amino acid residue (see paragraph 0027). Applicant is not in possession of the variants as broadly recited in claims 59-63 and 69 for the same reasons set forth above.

Claim Rejections - 35 USC § 112, 1st paragraph (Enablement)

6. The rejection of claims 1-8, 50-57, 59-63, and 65 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nanovesicle comprising a phospholipid selected from the group consisting of phosphatidylserine, phosphatidylethanolamine and structural analog thereof, and a polypeptide of SEQ ID NO.2 or a polypeptide having an amino acid sequence at least 95% identical to SEQ ID NO:2, does not reasonably provide enablement for a nanovesicle comprising a phospholipid selected from the group consisting of phosphatidylserine, phosphatidylethanolamine and structural analog thereof, and a polypeptide of SEQ ID NO:2 having one or more conservative substitutions or a biologically active variant of SEQ ID NO:2 is maintained.

The response states that methods for assaying whether the nucleotide sequences encode proteins that retain plasma membrane binding are known in the art and are also provided in the specification in working examples. Furthermore, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance in which the experimentation should proceed. In the present case, the quantity of experimentation required to practice the invention amounts to two steps: identifying a polypeptide comprising an amino acid sequence having at least 95% identity to SEQ ID NO: 2, and then assaying phospholipid nanovesicles incorporating the polypeptide for functional activity.

In light of panel decision from Pre-Appeal Brief Review, the rejection made to the part (a) of claim 1 and part (i) of claim 50, i.e. a polypeptide having an amino acid

sequence at least 95% identical to SEQ ID NO:2 is withdrawn. However, the rejection made to the part (b) of claim 1 and part (ii) of claim 50, i.e. a polypeptide having an amino acid sequence as set forth in SEQ ID NO:2 and having one or more conservative substitutions is maintained (emphasis added).

Applicant's arguments do not overcome the rejection to the part (b) of claim 1 and part (ii) of claim 50 because applicant argued only part (a) of the claims. As discussed above, the phrase "one or more conservative substitution" encompasses a change of one up to all amino acids of the SEQ ID NO: 2. Substitution many amino acid residues together would likely to affect the protein's structure thus the function. The specification does not provide guidance regarding which amino acids and how many of them can be changed in the wild type saposin C such that the resulting variants still have the anti-tumor activity. Based on the unpredictability of protein chemistry, lack of guidance, further in view of the breadth of the claims, it would require undue experimentation to make the broadly claimed variants having the required anti-tumor activity.

Applicant can overcome the rejection by cancelling the part (b) of claim 1 and part (ii) of claim 50, or amending the part (b) of claim 1 and part (ii) of claim 50 to further include a limitation of "at least 95% identical to SEQ ID NO:2".

It is noted that claims 59-63 and 69 (which were not rejected in the previous office action) are now included in this rejection for the recitation of "a biologically active variant of the amino acid sequence set forth in SEQ ID NO:1, the amino acid sequence set forth in SEQ ID NO:1 having one or more conservative substitutions" and "a

biologically active variant of the amino acid sequence set forth in SEQ ID NO:2, the amino acid sequence set forth in SEQ ID NO:1 having one or more conservative substitutions". The specification defines biologically active variants of a native prosaposin protein of the invention as variants having at least about 80%, 85%, preferably at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, and more preferably at least about 98%, 99% or more sequence identity to the amino acid sequence for the native protein, or may differ from that protein by as few as 1-15 amino acid residues, as few as 1-10, such as 6-10, as few as 5, as few as 4, 3, 2, or even 1 amino acid residue (see paragraph 0027). Applicant has not enabled the variants as broadly recited in claims 59-63 and 69 for the same reasons set forth above.

Claim Rejections - 35 USC § 103

7. The rejection of claims 1-8, 50-57, 59-63, and 65 under 35 U.S.C. 103(a) as being unpatentable over O'Brien (US 5,700,909, Date of Patent: 12/23/1997), in view of Liu et al. (WO 98/33482, Pub. date: 8/6/1998), and Habberfield (US 2002/0099001A1, Pub Date: 7/25/2002, earlier effective filing date 2/1/1995) is maintained.

The response states that The O'Brien reference teaches that peptides derived from Saposin C can be used to treat demyelination disorders while the present application describes that the combination of Saposin C and DOPS is necessary for the anti-cancer activity. Saposin C or its peptides alone have no killing effect on cancer cells. While O'Brien discloses that prosaposin or fragment thereof may be advantageously enclosed in a liposome-like (lamellar) structure, peptides delivered this

way only show use for nerve cell proliferation to counteract degeneration. In the present invention, SapC-DOPS, the lipid and protein freely combine to form nanovesicles. SapC is all across the membrane and not encapsulated. A lipid/saposin vesicle formed by the method of O'Brien will not exhibit anti-tumor activity as with the vesicles of the present invention. The examiner listed patents by Habberfield and Liu et al. for teaching liposomes composed of PS for drug delivery. As described above, anti-cancer effect requires both composition of DOPS and Saposin C. For example, replacement of DOPS with DOPC does not kill cancer cells while encapsulation of Saposin C in DOPS vesicle for delivery does not kill cancer cells. The results achieved in the present application are unexpected in light of the cited references.

The panel of Pre-Appeal Brief Review considered applicant's arguments with respect to Saposin C-DOPS are persuasive. The rejection to the embodiment of saposin C-DOPS is thus withdrawn. Applicant presented arguments only to this specific embodiment (saposin C- DOPS), however, the claims as written are not limited to this specific embodiment. Claims recite "phosphatidylserine, phosphatidylethanolamine and structures thereof" (see claims 1 and 50, for example), wherein the structures thereof include phosphatidic acid, phosphatidylglycerol, phosphatidylinositol, and phosphotidylserin (see claim 3). Therefore, claims encompass using a broad class of art known-phospholipids. While the examiner agrees that it is not obvious to pick DOPS from art disclosed phospholipids, however, it would have been obvious to use PE, PS and their structural analogues to make liposome because these phospholipids were wildly used for making drug delivery liposomes as shown by the teachings of Liu and

Habberfield. Furthermore, although the prior art does not disclose the antitumor activity of the liposome enclosed saposin C, the claims are drawn to a product, it is considered an inherent property of the claimed product.

Applicant can overcome the rejection by amending the claims to limit the phospholipid to DOPS.

Double Patenting

8. The rejection of claims 1-8 and 50-57 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 16, 17, 21 and 22 of U.S. Patent No. 6,872,406 in view of Vaccaro et al. (FEBS Lett. 1994, 349: 181-186, IDS) is maintained.

The response states a Terminal Disclaimer will be filed if conflicting claims are issued.

Since no Terminal Disclaimer has been filed, the rejection is maintained.

New Grounds of Objections and Rejections

Claim Objections

9. Claims 44-49, 59-63 and 65 are objected to because the claims are dependent from withdrawn claims.

10. Claim 7 is objected to for reciting "comprises at least 80 contiguous amino acids SEQ ID NO:2" because SEQ ID NO:2 only consists of 80 amino acids.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-8, 44, 47, 50-57, 59-63, and 65 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 7, 8, 21, 24, 29, 37-39, 42, 44 and 45 of copending Application No. 11/741,323. Although the conflicting claims are not identical, they are not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-3, 7, 8, 21, 24, 29, 37-39, 42, 44 and 45 of copending Application No. 11/741,323 disclose a composition comprising: a) a phospholipid, b) a safe and effective amount of an agent; and c) a fusogenic protein or polypeptide derived from

prosaposin and (d) a pharmaceutically acceptable carrier, wherein the fusogenic protein or polypeptide is saposin C, and the phospholipid is DOPS. The claims are further limited wherein the concentration of phospholipids is in at least 10-fold excess, by molar ratio, to that of the fusogenic protein or polypeptide, the size of liposomes is between 50-350 nanometers. As such claims 1-3, 7, 8, 21, 24, 29, 37-39, 42, 44 and 45 of copending Application No. 11/741,323 disclose every limitation of the instant claims 1-8, 44, 47, 50-57, 59-63, and 65.

13. Claims 1-3, 6, 7, 50-52, 55, and 56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 12/445,707. Although the conflicting claims are not identical, they are not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-10 of copending Application No. 12/445,707 are drawn to a composition comprising: an anionic phospholipid and a prosaposin-derived protein or polypeptide, wherein the phosphoplipid is DOPS, and the prosaposin-derived protein or polypeptide is saposin C.

14. Claims 1-8, 44-57, 59-63 and 65 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 37-

41 and 43-50 of copending Application No. 12/332,809. Although the conflicting claims are not identical, they are not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 37-41 and 43-50 of copending Application No. 12/332,809 disclose a composition comprising: a phospholipid and a polypeptide consisting of SEQ ID NO:2, wherein the phosphoplipid is DOPS, the molar ratio of the polypeptide to phospholipid is in the range from about 1:1 to about 1:50, the nanovesicle has a diameter in the range of 0.01 to 1 μm, the mass ratio of the polypeptide to DOPS is about 5:1, 15:7 or 15:1 to about 3:10, the composition comprises 10μM polypeptide and about 30μM DOPS, 10μM polypeptide and about 70μM. The amino acid sequence is 100% identical to the instant SEQ ID NO:2.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to HONG SANG whose telephone number is (571)272-8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Hong Sang/
Examiner, Art Unit 1643

/Larry R. Helms/
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